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In re: Patent Application of  
David F. Nicoli, et al  
Application No. 10/606,959  
Attorney Docket No. 6000  
Stability Assessment Of  
Dispersions And Emulsions

## INFORMATION DISCLOSURE STATEMENT

### REMARKS

Friberg et al provide estimates of the influence of the interparticle potential energy barrier height on the "half-life" of a simplified "emulsion" assuming droplets of a single size with an oil/water ratio of unity where the half-life is defined as the time needed for half of the original number of droplets in the emulsion to agglomerate, or coalesce. They conclude on page 66: "Calculations of the relative height of the barrier with electrolyte content are interesting from a scientific point of view, but of limited value in daily formulation efforts." They conclude at page 70 that: "The dilemma for the formulator of an emulsion lies in the fact that the success of a preparation can be judged only after a long time." It is said that this problem would be avoided if a reliable method for accelerated testing were found and concludes on page 71 that, "a general method of this kind is not available."

This major shortcoming is also emphasized by Breuer, who states: "Predicting long-term stability from accelerated laboratory tests still remains an elusive goal."

This lack of understanding of the variables that influence the onset of coalescence (instability) in emulsions is underscored by Walstra, who states on page 56 that much about

stability "is insufficiently known" and that prediction of combined instabilities is far more difficult.

The deficiency in knowledge concerning the basic interaction phenomena in complex emulsions, such as milk, is acknowledged by Euston et al.

Weiner recognizes the importance of emulsion stability, along with the apparent futility of accelerated stability testing, stating, "accelerated stability testing for coalescence is, at best, difficult and tricky" and that as to "predictive testing for coalescence of an emulsion there is little evidence that pushing the system far beyond what it will encounter in the market place yield any reliable information useful for shelf-life predictions."

From these references, it is clear that the principle unresolved problem in this art has been the prohibitively long time needed to determine the stability of a given emulsion or dispersion. This has led to attempts to accelerate the process of stability testing, centering around three means to accelerate the onset of instability: increasing the temperature, inducing strong shear forces, and centrifuging. These methods, for the most part, fail to yield unambiguous and consistently reliable quantitative information as to stability.

Newton reviews the effect of temperature on the rates of chemical reactions, and hence on the stability of dispersions, notably drug formulations.

The Kwan et al patent discloses determining the temporal stability of a reagent formulated as an emulsion. The emulsion is stressed at varying temperatures.

The Faure et al patent describes a method for determining the temperature stability of water-in-hydrocarbon emulsions as to phase separation including crystallization of paraffins in gas oils at certain temperatures. The onset of phase separation is detected by monitoring the weight variation of a gravimetric sensor.

Garver et al, U.S. Patent Number 6,263,725 describe the use of an on-line sensor based on UV-visible light absorption and scattering to detect and identify colloidal substances. The difference or ratio of light attenuation or scattering measurements performed at two or more temperatures provide a measure of the stability of the dispersion with respect to temperature.

Yoon et al also used the method of raising the temperature to assess emulsion stability. Thermal kinetic accelerated stability testing was conducted at 5, 20, 37, and 60°C, using multiple emulsion formulations and several means of particle size analysis is to detect changes in the PSD of the droplets over a period of two months. Although, in general, the number of days required to achieve the maximum measured mean diameter decreased with increasing temperature, there was a significant variation observed among the various emulsion formulations for some of the temperatures employed. The significant variability observed for most of the temperatures employed underscores the limitation associated with the use of temperature stress for quantitatively evaluating the stability of typical multi-component emulsions.

Vadas highlights the pitfalls associated with the use of elevated temperatures to accelerate stability assessment. The typical increase in temperature required to assess the stability of the emulsion may be large enough to cause the emulsion itself to change and convert the emulsion into a significantly different system, having a significantly different PSD. This is in sharp contrast with the desired goal of using temperature variation only as a means of perturbing the effectiveness of the net responsive interaction between neighboring charged particles or droplets, while the character of the emulsion is presumed to remain essentially unchanged.

A second approach that has been used to assess emulsion stability is the application of mechanical stress – e.g., “shaking” it in one form or another – in order to subject the dispersion

or suspension to shear forces. The application of shear forces is presumed to cause less stable emulsions to coalesce faster than more stable ones. For example, Degouy, et al, apply shear forces to muds used for oil drilling to determine their stability. However, in practice there are uncertainties and difficulties.

This can be appreciated by reviewing the communications between two pharmaceutical manufacturers in the Redhead et al and Mirejovsky et al letters. The validity of shake tests for providing a reliable measure of emulsion stability was disputed. Inconsistencies in the methods of mechanical agitation were noted. The earlier work of Hansrani et al acknowledged that oscillatory movement might cause emulsions to separate. It was said in the Mirejovsky letter that “a correlation between excessive shaking and the stability of an emulsion in real situations has never been established.”

Despite these difficulties, the Date et al patent describes a device for evaluating phase change in an emulsion, an emulsion pushed with a measured force. Changes in the measured force are used to evaluate the phase change of the emulsion. The Joseph et al patent also characterizes the dynamic stability of the emulsion based upon cycles of flow of the emulsion within a test vessel.

The Lamar et al patent describes methods for determining the stability of dietary emulsions by “watching and waiting,” and the application of thermal and mechanical stress (agitation in a Waring blender).

Vadas reviews the usefulness of centrifugation for assessing emulsion stability. While the use of a centrifuge serves to decrease greatly the time needed to achieve significant oil flotation, there is at least one serious shortcoming. The act of progressive sedimentation or flotation of the suspended droplets causes large changes in the local concentration of these

droplets. A large oil-concentration gradient develops over time in the emulsion possibly significantly changing its character.

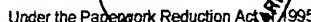
Kanicky et al demonstrate the gaps in knowledge in emulsion technology, pointing out that the majority of predictions as to stability of emulsions derive more from empirical observation than from theory.

Recent assessments by investigators, in different field of technology, draw attention to the shortcomings that exist in dispersion science. Euston et al, Mirejovsky et al, and Kanicky et al confirm that relatively little progress has been made in the prior art in applying theoretical models to observed emulsion stability. As is demonstrated in this application, the present invention discloses methods and apparatus which significantly accelerate the onset of instability in dispersions and emulsions when compared with the techniques taught and practiced in the prior art, as shown in the aforementioned prior art.

Respectfully submitted,

A handwritten signature in black ink, reading "Milton M. Field". The signature is written in a cursive, flowing style with a large, prominent "M" and "F".

Milton M. Field  
Reg. No. 20,262



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Filing Date	06-27-03
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First Named Inventor	Nicoli
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Art Unit	2856
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Examiner Name

Attorney Docket Number	6000
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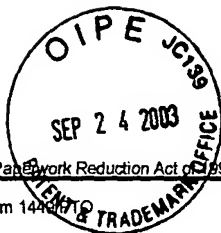
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		FRIBERG, et al, "Theroy of Emulsions" (in Pharmaceutical Dosage Forms: Disperse Systems, Lieberman, et al (eds.), Vol. 1), 1988, pp. 49, 63, 66, 70-71.	
		BREUER, "Cosmetic Emulsions" (in Encyclopedia of Emulsion Technology, Becher (ed.) Vol. 2), 1985, pp. 385, 420.	
		WALSTRA, "Emulsion Stability" (in Encyclopedia of Emulsion Technology, Becher (ed.) Vol. 4), 1996, pp. 1, 56-57, 119.	
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		REDHEAD, et al, Am. J. Health-Syst Pharm., Vol. 57, 2002, pp. 1174, 1176.	
		MIREJOVSKY, et al, Am. J. Health-Syst. Pharm., Vol. 57, 2002, pp. 1176-1177.	

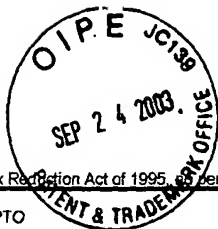
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		HANSRANI, et al, J. of Parenteral Science and Technology, Vol. 37, 1983, pp. 145-150.	
		KANICKY, et al, Handbook of Applied Surface and Colloid Chemistry, Vol. 1, 2001, pp. 251, 257.	

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